DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/06/2010 has been entered.

2. Currently, claims 21-28 are pending in the instant application. Claims 1-20 and 29-221 have been canceled. Claim 21 has been amended. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented. The rejections previously presented in the office action mailed 09/16/2010 have been withdrawn due to the amendment to the claims and applicants remarks filed 12/06/2010. Specifically example 6 and table 14 provide support for the amendment to the claims. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The disclosure is objected to because of the following informalities: the specification points to figure 4 for confirmation of melanoma specific genes by RT-PCR however this should

be figure 5 not figure 4, see pg 48, line 17. The specification points to figure 4a and 4b to demonstrate differences in expression of PLAB and L1CAM however this should be figure 5a and 5b, see pg. 50 lines 21.

Appropriate correction is required.

Claim Objections

4. Claim 25 is objected to because of the following informalities: claim recites where in the fluorophores correspond to tyrosinase: C1, PBGD: Cy5, where applicable however none of the preceding claims require or recite the genes tyrosinase or PBGD as these genes were non-elected. Appropriate correction is required.

Claim Rejections - 35 USC § 112- 2nd Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 21-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites "(relative to normal skin cells)". The metes and bounds of the recitation "(relative to normal skin cells" is unclear, it is not clear if this is an intended limitation of the claim or if this is merely an example of possible over expression level. None of the preceding steps require determining expression of normal skin cells or a biological sample that is a skin cell. Thus the limitations of relative to normal skin cells is indefinite as it is not clear what is

encompassed by over expression (relative to normal skin cells) and this recitation is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 21-22 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon (US Patent 6057105, cited on IDS) In view of van der Velden (Int J Cancer (2003) 106:472-479) in view of Thies (Eur J Cancer (2002), 38:1708-1716, cited on IDS).

Hoon teaches methods for detection of melanoma by extracting nucleic acid from a biological sample wherein the nucleic acid targets are from at least two carcinoma marker genes that are amplified (see column 2 lines 61-65). Hoon teaches amplification by PCR, specifically

RT-PCR (see column 3, lines 18-20) (claim 26) on biological samples that include human tissue (see column 3, lines 27-36). Hoon teaches the use of two different primer pairs specific for two different specific markers and following detection of specific markers, comparison of results to an normal population is performed (See column 4, lines 37-44) and internal control (see column 17, lines 36-40) (claim 27). Hoon teaches any marker that is correlated with the presence of melanoma may be used and teaches where a particular combination of markers is highly specific for melanoma, the statistical significant of a positive result will be high (see column 4 line 46-62). However, Hoon does not teach analysis of both PLAB and L1CAM expression in human tissue samples.

Van der Velden teaches expression analysis of uveal melanoma development. Van der Velden teaches MIC1 (PLAB) is over expressed in primary uveal melanoma cell line by over 5 fold (see table 1).

Thies teaches obtaining tissue samples from patients with melanoma and with benign melanocytes (See 2.2 and 2.3, pg 1709). Thies teaches analysis of L1CAM expression in melanocytes and melanoma. Thies teaches no L1 reactivity was identified in melanocytes (See figure 3) while positive melanoma cells showed intense expression of L1CAM (see 3.1, pg. 1711). Thies teaches L1CAM is a predictive marker for melanoma (see table 1 and 2). Thus, Thies demonstrates increased expression of L1CAM in human tissue samples of melanoma compared to normal skin cells.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of determining melanoma in a human tissue sample using known molecular melanoma markers as taught by Hoon and include additional

known markers including M1C1 and L1CAM, as MIC1 and L1CAM are known melanoma molecular markers, as taught by van der Velden and Thies. The ordinary artisan would have been motivated to improve the method of detecting nucleic acid corresponding to melanoma to identify melanoma, as taught by Hoon to include analysis of additional molecular markers because Hoon teaches multiple markers provide increased sensitivity over existing methods and teaches that any known marker correlated with melanoma can be used in the method. van der Velden teaches multiple known markers correlated with melanoma, including MIC1 and Thies teaches L1CAM is a known molecular marker of melanoma, thus the ordinary artisan would have had been motivated based on the teaching of Hoon in view of the knowledge that MIC1 and L1CAM are known markers for melanoma taught by van der Velden and Thies, to include analysis of these markers in the method of Hoon to identify melanoma. Both van der Velden and Thies teach markers that are statistically correlated with melanoma, thus the ordinary artisan would have had a reasonable expectation of success that the use of the markers disclosed by van der Velden, including MIC1 and the marker L1CAM taught by Thies could be used in the method of Hoon because Hoon teaches any marker that is correlated with melanoma can be used and markers that are highly specific for melanoma will have a higher positive result. Furthermore, the ordinary artisan would have had a reasonable expectation of success that a fifteen fold increase in expression detected in the method of Hoon in view of van der Velden and Thies would identify melanoma because Hoon teaches the presence of molecular markers teach identification of melanoma relative to normal patients, Thies teaches overexpression of L1CAM and van der Velden teaches at least a fivefold increase of MIC1 in melanoma, thus a fifteen fold increased would be even more conclusive result of identification of melanoma.

Because Hoon, van der Velden, and Thies teach identification of melanoma by molecular marker expression analysis, it would have been obvious to one skilled in the art to combine known elements, the known molecular markers of L1CAM and MIC1 as taught by van der Velden and Thies, to known method of Hoon to yield the predictable result of identification of melanoma by measuring gene expression in human tissue using known prior art elements, including molecular markers of L1CAM and MIC1.

Hoon in view of van der Velden and Thies does not teach the PCR products comprising SEQ ID NO 25 and 26. However, to practice the method of Hoon in view of van der Velden and Thies, the ordinary artisan would be motivated to generate different primers to detect the MIC1 and L1CAM gene which would yield the PCR products of SEQ ID NO 25 and 26 for detection of melanoma by RT-PCR in the method Hoon in view of van der Velden and Thies. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested new primers or probes to obtain PCR products that comprise SEQ ID NO 25 and 26 to identify melanoma and identify oligonucleotides with improved properties. Thus, for the reasons provided above, the ordinary artisan would have designed additional primers and probes to obtain PCR products

comprising SEQ ID NO 25 and 26, using the teachings in the art at the time the invention was made.

10. Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon in view of Van der Velden and Thies as applied to claim 21-22 and 26-27 above, and further in view of Slepnev (US 2003/0235844A1).

The method of Hoon in view of van der Velden and Thies is set forth in section 9 above. Hoon in view of van der Velden and Thies does not teach PCR products comprising fluorophores including FAM and Texas Red.

However, it was well known in the art for analysis of real time gene expression profiling to use PCR products comprising fluorophores including FAM and Texas Red. Slepnev teaches monitoring amplification of one or more nucleic acid sequences by incorporation of one or more fluorophores (see para 69). Slepnev teaches fluorescent markers including FAM and Texas Red (See para 131). Slepnev teaches the detected fluorescent signal strength can be recorded and used to determine the relative ratio of each target sequence (see para 133). Slepnev teaches real-time PCR for gene expression profiling allows for improved determination of abundance of one or more target nucleic acids, especially target RNA species in original samples (See abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Hoon in view of van der Velden and Thies of identifying melanoma by gene expression profiling in tissue samples of markers including MIC1 and L1CAM by RT-PCR to include real-time PCR using fluorophores including FAM and Texas Red as taught by Slepnev. The ordinary artisan would have been motivated to

improve the method of Hoon in view of van der Velden and Thies to include a non-fluorophore labeled PCR products and real-time PCR analysis as taught by Slepnev because Slepnev teaches that by doing so allows for improved determination of abundance of one or more target nucleic acids. Furthermore, Slepnev demonstrates the use of FAM and Texas Red as fluorophores, thus the ordinary artisan to practice the method of Hoon in view of van der Velden and Thies and further in view of Slepnev would have been motivated to generate different PCR products including PCR products of MIC1 with FAM fluorophore and L1CAM with Texas Red fluorophore, which would yield predictable results of detecting melanoma by expression analysis of L1CAM and MIC1.

11. Claims 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon in view of van der Velden and Thies as applied to claims 21-22 and 26-27 above, and further in view of Copois (Lab Inv, 2003, vol 83, vol 4, pp 599-602)

The method of Hoon in view of van der Velden and Thies is set forth in section 9 above. Hoon in view of van der Velden and Thies does not teach RNA extracted by homogenizing sample, contacting RNA to substrate containing RNA binding materials, washing substrate and eluting bound RNA.

However, it was well known in the art to isolate RNA from tissue samples by homogenizing sample, contacting RNA to substrate containing RNA binding materials, washing substrate and eluting bound RNA. Copois teaches a melanoma tumor sample was extracted using procedure of RNeasy Mini kit, which encompasses homogenizing the sample, contacting

homogenate with silica column, binding RNA to column, and eluting RNA from column (see pg. 599, 1st column). Copois teaches isolation of RNA for detection of two different mRNA levels by RT-PCR and teaches efficiency for two genes was >90% (see figure 2)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Hoon in view of van der Velden and Thies of identifying melanoma by gene expression profiling in tissue samples of markers including MIC1 and L1CAM by RT-PCR to include isolation of RNA by RNeasy mini kit as taught by Copois. The ordinary artisan would have been motivated to improve the method of Hoon in view of van der Velden and Thies to include isolation of RNA by RNAeasy mini kit as taught by Copois because Copois teaches by doing so allows for an efficient PCR amplification of two different genes.

Conclusion

12. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Sarae Bausch/
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